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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,280	09/30/2003	Timothy R. Billiar	14022-011001	7071

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EXAMINER	
FUBARA, BLESSING M	
ART UNIT	PAPER NUMBER
1618	

NOTIFICATION DATE	DELIVERY MODE
01/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/676,280	BILLIAR ET AL.	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,21-40 and 55-65* is/are pending in the application.

4a) Of the above claim(s) *4-9 and 21-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,10,11 and 55-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The prosecution in this application is reopened in view of the conference decision of the Pre-Appeal conference held 10/14/09.

1. Applicant's arguments, in the Pre-Appeal Brief Request, see pages 1-5, filed 9/15/09, with respect to the rejection(s) of claim(s) 1-3, 10 and 11 under 35 U.S.C. 102(b) as being anticipate by Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001); claims 1-3, 10, 11 under 35 U.S.C. 102(e) as being anticipated by Pinsky et al. (US 2005/0048133 A1); claims 1, 55 and 56 under 35 U.S.C. 103(a) as being unpatentable over Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001) or Pinsky et al. (US 2005/0048133 A1); claims 1, 2 and 57-65 under 35 U.S.C. 103(a) as being unpatentable over Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001) or Pinsky et al. (US 2005/0048133 A1) in view of Peitzman et al. ("Hemorrhagic shock" in Curr Probl Surg. 1995 Nov. 32 (11): 925-1002 , abstract); have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, new ground(s) of rejection is made in view of Fujita or Pinsky in view of Carceller or Neely and further in view of Peitzman or Bach (see rejections below).

2. Applicant's argument has to do with treating hemorrhagic shock v. treating ischemia. The rejection has been modified using secondary references to provide treatment for hemorrhagic shock. Applicant's argument therefore as it relates to the differences between ischemia and hemorrhagic shock as applied in the last office action is thus moot.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-3, 10, 11 and 57-65 are rejected under 35 U.S.C. 112, first paragraph for reasons of record and reiterated herein below, because the specification, while being enabling for certain specific concentration of CO effective to treat hemorrhagic shock, does not reasonably provide enablement for all concentration CO effective to treat hemorrhagic shock. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is scope of enablement.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient number of the factors are discussed below for a *prima facie* case.

1) Nature of the invention

The nature of the invention is the administration of carbon monoxide to a patient in order to treat hemorrhagic shock.

2) State of the prior art

Carbon monoxide (CO) is known in the art to be toxic to humans causing exhaustion and headache at levels of as low as 70 ppm (Omaye, "Metabolic modulation of carbon monoxide toxicity," in Toxicology 180 (2002) 139-150). The instant specification at paragraph [0040] talks about using Co at levels of 10 ppm to 3000 ppm for the treatment of hemorrhagic shock.

3) The predictability or lack thereof in the art

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific guidance is required to enable the artisan to practice the full scope of the claimed invention.

In the instant case, the scope of the claimed invention spans all concentrations of CO for effectively treating hemorrhagic shock. Also while the instant disclosure at paragraph [0040] envisions the use of 10-3000 ppm CO for inhalation, the prior art describes CO to be toxic at levels of as low as 70 ppm.

4) Amount of direction and guidance present

The direction and guidance provided is limited to amounts described in paragraph [0040] and not to all possible amounts. The listing of the amounts of CO at paragraph [0040] is an invitation to experiment because (see 5 below).

5) The presence or absence of working Examples

The working examples fail to provide any amount of CO useable in the invention, and by implication then refers back to the amounts disclosed in paragraph [0040]. The working examples do not correlate with the scope of the claims.

6) Quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine what concentration of CO to use that would not provide toxicity since applicants envision concentrations of 10-3000 ppm and Omaye discloses that CO levels of 70 ppm is toxic ands the claims is open ended to any amount of CO.

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation to test and use the scope of the claimed invention encompassed in instant claims, with no assurance of success.

This rejection may be overcome by reciting the concentrations of CO effective for the claimed method.

NB: No arguments were presented in the Pre-Appeal Brief filed 9/15/09 against the above rejections and therefore no response is also presented.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001) or Pinsky et al. (US 2005/0048133 A1) in view of Carceller et al. (US 5,420,131) or Neely (US 5,504,090).

8. Fujita discloses that inhaled CO protects against ischemic lung tissue injury (see the whole document with emphasis on the abstract; page 601, left column, three lines from the bottom). Fujita uses CO composition that is blended with room air and the air blended with

room air is administered by inhalation (page 602, right column 4th full paragraph). The CO blended with room air meets the composition of claim 1 and inhalation meets claim 3.

9. Fujita teaches treating ischemic injury. Fujita does not teach treating hemorrhagic shock. But, ischemia and hemorrhagic shock have been known to be treated by the same compositions. For example, Neely teaches method of treating ischemia and reperfusion, sepsis, anaphylaxis, hemorrhagic shock and trauma in patients in need thereof with the inventive composition of Neely (see column 6, lines 24-29). Also, Carceller treats septic shock, anaphylactic shock, hemorrhagic shock and myocardial ischemia in a mammal in need thereof by administering an effective amount of the compound of Carceller (see claim 13).

10. Therefore, taking the teaching of Fujita and Carceller or Neely, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success that administration of the composition comprising CO to a mammal/subject in need thereof would effectively treat ischemic injuries or hemorrhagic shock since these conditions have been known to be treatable by the same compositions or compounds.

11. Pinsky teaches method of treating ischemic disorder in a subject in need thereof by administering carbon monoxide gas or mixture of CO and inert gases such as air, oxygen, nitrogen and argon in sufficient amount over sufficient period of time (paragraphs [0055], [0056], [0057], [0058]-[0061]) by inhalation or by extracorporeal exposure to blood or body fluids. The CO mixed with the inert gases meets the limitation of the composition of claim 1. Administration by inhalation meets the administration of claim 1 and administration by inhalation of claim 3.

12. Pinsky teaches treating ischemic injury. Pinsky does not teach treating hemorrhagic shock. But, ischemia and hemorrhagic shock have been known to be treated by the same compositions. For example, Neely teaches method of treating ischemia and reperfusion, sepsis, anaphylaxis, hemorrhagic shock and trauma in patients in need thereof with the inventive composition of Neely (see column 6, lines 24-29). Also, Carceller treats septic shock, anaphylactic shock, hemorrhagic shock and myocardial ischemia in a mammal in need thereof by administering an effective amount of the compound of Carceller (see claim 13).

13. Therefore, taking the teaching of Pinsky and Carceller or Neely, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success that administration of the composition comprising CO to a mammal/subject in need thereof would effectively treat ischemic injuries or hemorrhagic shock since these conditions have been known to be treatable by the same compositions or compounds.

14. Claims 1, 2, 10, 11 and 57-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001) or Pinsky et al. (US 2005/0048133 A1) in view of Carceller et al. (US 5,420,131) or Neely (US 5,504,090) and further in view of Peitzman et al. ("Hemorrhagic shock" in Curr Probl Surg. 1995 Nov. 32 (11): 925-1002 , abstract).

15. Fujita and Pinsky in view of Carceller or Neely have been shown above to render obvious the method of claims 1 and 3. Fujita and Pinsky in view of Carceller or Neely does not teach further transfusion of blood to treat the ischemic condition in addition to the CO. However,

Peitzman teaches that transfusion of blood is effective to treat hemorrhagic shock including ischemia; Peitzman is clear that treatment and evaluation must be simultaneous to evaluate organ and organ response, tissue damage, etc; blood circulation must be restored in which adequate red blood cell mass with its oxygen carrying capacity must be restored (see page 981, beginning at the 3rd full paragraph under treatment of hemorrhagic shock to paragraph bridging pages 983 and 984). Peitman's critical evaluation and assessment of the condition meets claims 10 and 11. The transfusion meets claims 2 and 57 and blood transfused contains whole blood, red blood cells, platelets, plasma and coagulation factors since these are all components of blood so that claims 58-65 are met. Therefore, taking the combined teachings of Fujita, Pinsky, Carceller, Neely and Peitzman, one having ordinary skill in the art at the time the invention was made, would have reasonable expectation of success that combining blood transfusion with CO administration would effectively treat ischemia and/or hemorrhagic shock.

16.

17. Claims 1, 55 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001) or Pinsky et al. (US 2005/0048133 A1) in view of Carceller et al. (US 5,420,131) or Neely (US 5,504,090) and further in view of Bach et al. (US 2003/0039638).

18. Fujita and Pinsky in view of Carceller or Neely have been shown above to render obvious the method of claim 1. Pinsky describes exposing the subject to the CO for 12 hours (see paragraph [0028], [0058]) so that with respect to claim 56, the artisan would be motivated to expose the subject to the CO that would produce the goal of treating the ischemia or hemorrhagic

shock since same compositions have been known to treat ischemic conditions and hemorrhagic shock. Fujita or Pinsky does not teach the ppm concentration of the CO in claim 55. But, Bach teaches that a subject in need thereof is exposed to levels of CO at 250 ppm (see paragraphs [0007], [0061], [0102], [0107], [0118], [0243] and [0265]) to treat ischemic conditions. Therefore, taking the teachings of Fujita or Pinsky in view of Carceller or Neely, and the suggestion by Bach to maintain the CO at level of 250 ppm, one having ordinary skill in the art at the time the invention was made would reasonably expect that exposure of the subject to CO at 250 ppm would be effective in treating ischemia or hemorrhagic shock.

Response to Arguments

19. Applicant's arguments filed 9/15/2009 have been fully considered have been found to be persuasive as it relates to the differences between hemorrhagic shock and ischemia. New rejections were made as described above.

20. Declaration by Dr. Brian Zuckerbraun:

21. Applicant's allegation that the office refused to consider the declaration by Dr. Zuckerman is both unfortunate and unfair because the office action of 4/16/2009 addressed the declaration on page 14 of the office action and it is hereby reproduced below for applicant (action is also on pair):

22. Declaration of Dr. Brian Zuckerbraun under 37 CFR 1.132: (from page 14 of the office action of 4/16/09)

23. The declaration under 37 CFR 1.132 filed 1/12/09 is insufficient to overcome the rejection of claims 1-3, 10 and 11 based upon rejections under 35 USC 102(b) by Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001) as set forth in the last Office action because: Declaration can not be used to overcome rejections under 35 USC 102.

24. The declaration under 37 CFR 1.132 filed 1/12/09 is insufficient to overcome the rejection of claims 1-3, 10 and 11 based upon rejections under 35 USC 102(e) by Pinsky et al. (US 2005/0048133 A1) as set forth in the last Office action because: Declaration can not be used to overcome rejections under 35 USC 102.

25. The declaration under 37 CFR 1.132 filed 1/12/09 is insufficient to overcome the rejection of claims 1, 2 and 55-65 based upon rejections under 35 USC 103 over Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001) and Pinsky et al. (US 2005/0048133 A1) as set forth in the last Office action because: While Dr. Zuckerbraun declares that ischemia and hemorrhagic shock are distinct medical conditions, Dr. Zuckerbraun has not provided an opinion that ischemia cannot occur in hemorrhagic shock and has not presented factual showing that ischemia cannot occur in hemorrhagic shock.

26. It is thus unclear what would have constituted a consideration by applicant's standard. A rejection under 35 USC 102 cannot be overcome by declaration under 37 CFR 1.132.

27. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on Monday to Thursday from 7 a.m. to 5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Blessing M. Fubara/
Primary Examiner, Art Unit 1618